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Toward optimal mechanical ventilation of the injured lung: the role of expiratory duration

Jason H.T. Bates[1*], Michaela Kollisch-Singule[2], Donald P. Gaver[3] and Gary F. Nieman[4]

Abstract
Positive pressure mechanical ventilation is a life-saving intervention for patients with acute respiratory distress syndrome (ARDS), but it can also increase mortality by causing ventilator-induced lung injury (VILI) if applied inappropriately. Although strategies like low-tidal volume ventilation and prone positioning have been shown to reduce mortality, the optimal patient-specific approach to mechanical ventilation in ARDS has yet to be identified. The worst manifestations of acute lung injury arise when fluid and proteins from the blood leak through a damaged blood-gas barrier, accumulating in the airspaces and impairing the ability of pulmonary surfactant to lower surface tension. This amplifies the ventilatory stresses in the lung tissues, which further damages the blood-gas barrier, leading to a vicious cycle of worsening injury. Studies suggest that VILI may be most effectively avoided by preventing the atelectrauma caused during inspiration by the forced reopening of lung units that close during each expiration. Atelectrauma is conventionally mitigated with positive end-expiratory pressure (PEEP), but it remains unclear if the algorithmic selection of PEEP leads to mortality reductions in ARDS. Animal studies, however, support the efficacy of exploiting the time-dependent nature of recruitment and derecruitment, for example through the use of brief expiratory durations that continually adapt to changing lung mechanics. Despite decades of research, it remains unclear how to minimize VILI in any given ARDS patient. Animal studies coupled with energy dissipation analysis indicate that the prevention of VILI requires, above all, avoidance of the atelectrauma caused by cyclic recruitment and derecruitment in the lung. In addition, the path to optimal mechanical ventilation in ARDS must be based not only on the amplitudes of the pressures applied to the lung but also on their temporal natures.

Keywords Volutrauma, Atelectrauma, Ventilator-induced lung injury, Positive end-expiratory pressure, Acute respiratory distress syndrome

Background

Up to 40% of the 200,000 patients with acute respiratory distress syndrome (ARDS) in the US each year do not survive [1]. Public awareness of the devastation wrought by ARDS has significantly increased since 2020 because of its role in the morbidity and mortality of severe SARS-CoV-2 disease [2]. Currently there are no preventive medical therapies for ARDS, so management remains purely supportive [3]. Central to this support is positive pressure mechanical ventilation, but this potentially life-saving intervention is a double-edged sword that can also increase fatality when it leads to ventilator-induced

*Correspondence:
Jason H.T. Bates
jason.h.bates@med.uvm.edu
[1]Department of Medicine Larner College of Medicine, University of Vermont, Burlington, VT 05405, USA
[2]Department of Surgery, University of Arkansas Medical Sciences, Little Rock, AR 72205, USA
[3]Department of Biomedical Engineering, Tulane University, New Orleans, LA 70118, USA
[4]Department of Surgery, SUNY Upstate Medical University, Syracuse, NY 13210, USA

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lung injury (VILI). Accordingly, recent efforts have been made to avoid invasive mechanical ventilation in favor of other techniques such as high-flow nasal cannula [4] and noninvasive ventilation methods such as continuous or biphasic positive airway pressure [5].

When mechanical ventilation is necessary, however, the only base of evidence for its use in ARDS is low-tidal volume (low-V_T) ventilation [6], and prone positioning [7]. There is also some evidence that avoidance of high driving pressure is also beneficial [8], although this has yet to be proven definitively. Unfortunately, mortality from ARDS has remained essentially stable since the ARDSnet trial [9, 10]. Even the case for some level of positive end-expiratory pressure (PEEP) remains equivocal despite its physiologic rationale being beyond dispute. No trial has yet demonstrated a reduction in mortality by any algorithm for selecting PEEP [11, 12], although some meta-analyses suggest otherwise [4, 13].

These various factors nurture the conviction that we have yet to find the best way to mechanically ventilate patients with ARDS. Identifying an optimal strategy has proven challenging because of the plethora of pathophysiologic considerations pertinent to VILI. In this Perspective, we systematically explore these considerations to identify potential research directions that may help to optimize mechanical ventilation in a patient-specific manner.

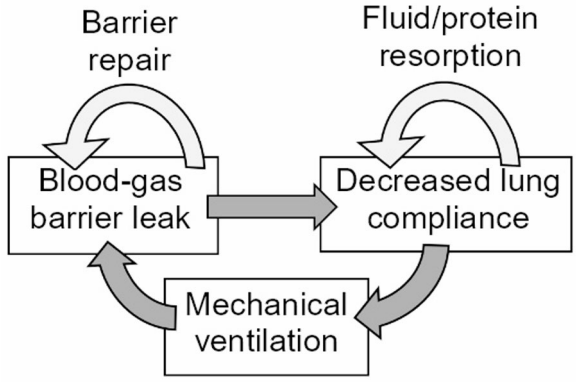

Fig. 1 Ventilator-induced lung injury (VILI) is caused by the tissue stresses and strains induced by mechanical ventilation. These injurious factors cause plasma-derived fluid and proteins to leak through a damaged blood-gas barrier where they flood alveoli and interfere with the surface tension-lowering properties of pulmonary surfactant. This causes lung compliance to decrease, which augments tissue stresses and makes VILI worse in a vicious cycle (dark gray arrows). At the same time, innate mechanisms seeking to repair the leak in the blood-gas barrier together with removal of airspace fluid via the lymphatic system work to reverse the damage of VILI (light gray arrows)

The VILI endgame: winning the battle between injury and repair

Despite having a dismal prognosis, most ARDS patients eventually survive [14] thanks to their innate abilities to heal despite the collateral VILI incurred during mechanical ventilation. In essence, ARDS survivors triumph in the battle between injury and repair [15]. The balance between these competing forces is delicate, however, so anything that tips it in favor of repair could significantly impact ARDS survival.

Endothelial leak is a cardinal feature of most forms of ARDS [16], especially those with an inflammatory etiology in which movement of inflammatory cells from the vasculature to the tissue is a natural part of the host response. This leads to accumulation of blood-derived fluid, cells, and proteins in the parenchymal interstitium. The worst manifestations of acute lung injury arise, however, when fluid and proteins from the blood leak through a damaged blood-gas barrier and accumulate in the airspaces. Here, they flood alveoli and interfere with the crucial ability of pulmonary surfactant to dynamically lower surface tension at the air-liquid interface [17]. The resulting increases in surface tension cause localized decreases in lung compliance that focally amplify the tissue stresses imposed by mechanical ventilation [18]. This, in turn, damages the blood-gas barrier even further, worsening the alveolar leak in a vicious cycle of increasing VILI that spirals toward severe ARDS (Fig. 1).

The pulmonary epithelium thus serves as the last line of defense between the vasculature and the pulmonary airspaces, so protecting its integrity is a key consideration in avoiding VILI. If the blood-gas barrier is compromised, it is crucial to minimize the leakage of plasma-derived material so that natural healing mechanisms are not overwhelmed. Healing requires both the repair of perforations in the blood-gas barrier and the clearance of detritus from the airspaces (Fig. 1) [19]. Minor tears in the epithelial cell membrane often spontaneously reanneal with few lasting consequences [20]. More severe damage, however, leads to cellular apoptosis or necrosis. Repair of this injury occurs over the longer timescale that is required for cell migration and division. However, this may lead to chronic morbidity associated with fibrosis [21]. In the meantime, lymphatic drainage is essential for removal of airspace fluid [22] and depends on a balance between hydrostatic and oncotic pressures [23] modulated by the cyclic pressures imposed by mechanical ventilation [24].

Minimally injurious mechanical ventilation: personalized and adaptive

ARDS exhibits significant pathophysiological variation between patients due to its various proximal causes and the natural variation in patient physiology [25]. ARDS

is also a dynamic condition that waxes and wanes over time. For example, a respiratory viral infection begins with symptoms that are typically quite manageable in their early stages but may eventually develop into respiratory failure. Once a patient is in full-blown ARDS, the mechanical ventilation strategies needed to keep them alive will likely differ from those appropriate during recovery. For example, low-V_T ventilation has been shown to reduce ARDS mortality compared to more conventional tidal volumes [6]. However, this can lead to elevated partial pressures of arterial carbon dioxide that may be difficult to tolerate and require sedation to relieve patient-ventilator dis-synchrony [26]. Such draconian measures may be appropriate for a patient whose life hangs in the balance, but they can be relaxed as the patient approaches readiness for extubation [27].

These considerations highlight that an optimal mechanical ventilation strategy for ARDS must be tailorable to individual patients and adaptable to evolving conditions. A one-size-fits-all approach that is best for the population on average can be highly suboptimal for an individual [28]. This raises the question as to what exactly is meant by the term "*optimal*." The usual answer to this question is "*that which minimizes mortality*." Given that there is an essentially limitless number of ways in which mechanical ventilation can be applied to achieve a given alveolar minute ventilation, it is not practical to blindly search through the possibilities. The search must be linked to the underlying mechanisms that ultimately determine mortality. In this sense, a more helpful definition of "*optimal*" is "*that which minimizes VILI*". This definition allows for a more biomechanistic and targeted search for the best ventilation strategy.

To proceed along these lines, it is necessary to be able to link the stresses and strains of mechanical ventilation to a quantitative prediction of the amount of VILI that accrues. That is, we need a VILI *cost-function*, based on appropriate biomarkers, that can be used in real time to adjust mechanical ventilation to minimize the aggregate VILI [29]. Numerous biomarkers of VILI can be used clinically to assess the injury status of a ventilated patient. Computed tomography, for example, provides a great deal of specific information about lung structure that reflects the progress and consequences of VILI [30, 31], but it cannot be performed often enough to inform minute-by-minute ventilator adjustments. The situation for blood gas analysis is similar. On the other hand, the assessment of changes in lung mechanics can be performed continuously simply by monitoring airway pressure and flow [32, 33]. These considerations suggest that the practical maintenance of optimal mechanical ventilation in real time will likely be based on a VILI cost function derived from P and $\dot{V}$ [29].

Staying safe in the V_T-PEEP plane

VILI is thought to arise from two distinct biophysical mechanisms. One is the intuitively obvious process whereby tissues become damaged from overdistension. Any elastic material will eventually sustain structural damage if subjected to sufficient strain, and the lung parenchyma is no exception. The damage caused by overdistending the lung through excessive inflation is called volutrauma. Of course, the mammalian lung has evolved to experience substantial and frequent changes in lung volume during breathing. Consequently, volutrauma is not easily produced in a healthy lung, even when tidal volumes are very large [34]. However, when the lung becomes injured, whether primarily from a direct insult or secondarily from an event occurring somewhere else in the body, its ability to sustain a change in volume without injury can be significantly compromised [35].

The other type of VILI is linked to the phenomenon of alveolar collapse, or atelectasis, and is known as atelectrauma. When air is displaced from alveoli and/or small airways, their opposing internal surfaces, which are lined with fluid, come into contact. Reopening these structures requires that air be forced into what is effectively a fluid glue holding the surfaces together. This requires high local forces that can damage the underlying epithelium, particularly when repeated with every breath [36]. Experimental evidence from animal models suggests that cyclic recruitment and derecruitment (R/D) of closed lung units may be more damaging to the lung tissue than overdistension, and that the two processes synergize when present simultaneously [34]. A possible reason for this synergy is that tissue stresses become greatly amplified at interfaces between open and consolidated lung regions [17, 18]. Theoretical considerations and animal experiments also support the idea that VILI is governed by the amount of energy dissipated in the lung tissues due to cyclic R/D [36]. In contrast, the potential energy temporarily stored in tissue elastic recoil is irrelevant [37].

These findings suggest the possibility that it may be more important to avoid the atelectrauma caused by R/D than the volutrauma caused by overdistension, even though reducing tissue distension is the primary goal of low-V_T ventilation. In fact, the conventional strategies used to avoid volutrauma and atelectrauma are fundamentally at odds. Cyclic R/D occurs in a normal lung below closing volume, which is normally below functional residual capacity. As the lung becomes increasingly injured, the accumulation of airspace fluid and the development of surfactant dysfunction cause the closing volume to increase progressively [38], increasing the likelihood of cyclic R/D occurring during mechanical ventilation. The conventional way to prevent this is to apply an appropriate level of PEEP, but this elevates mean airway

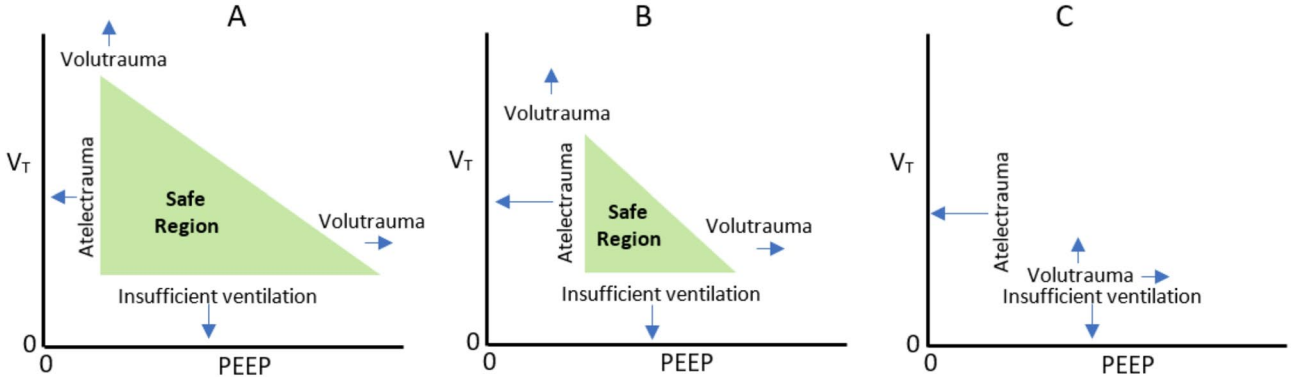

Fig. 2 The progression of the "safe region" for mechanical ventilation in the V_T-PEEP plane. **A**) Normal lung with a large safe region. **B**) Moderately injured lung with a reduced safe region. **C**) Severely injured lung for which there is no safe region

pressure and thus works against the avoidance of volutrauma in patients without recruitable lung units.

A helpful, albeit simplified, way to understand the conventional options available to ventilate the lung safely is via the V_T-PEEP plane [34], illustrated conceptually in Fig. 2. Any given pair of values of V_T and PEEP corresponds to a single point in this plane. There is wide latitude in the choice of V_T and PEEP when it comes to safely ventilating the normal lung. Such latitude is represented by a relatively large "safe region" in the V_T-PEEP plane from which V_T and PEEP can be selected without leading to VILI (Fig. 2A). VILI occurs when venturing outside the safe region, leading to volutrauma when end-inspiratory lung volume becomes too high, atelectrauma when end-expiratory lung volume becomes too low, and hypercapnia when V_T is too low to sustain adequate ventilation. When the lung becomes injured, however, the maximum volume it can sustain without volutrauma is reduced, while the lung volumes at which R/D begins to occur are increased. These factors reduce the area of the safe region (Fig. 2B), significantly limiting the choices of non-injurious V_T and PEEP. When lung injury becomes severe enough, the safe region may disappear altogether (Fig. 2C), in which case VILI becomes inevitable. In other words, mechanical ventilation regimens that are safe for a normal lung may no longer be safe once the lung becomes injured [34]. Of course, Fig. 2 neglects other factors that can influence VILI such as respiratory rate and changes in recruitment with PEEP, but it serves to highlight the importance of identifying patients at risk for ARDS and preemptively ventilating them safely. Otherwise, it may become an issue of "closing the barn door after the horse has bolted" [39].

Recruitment and derecruitment depend on time as well as pressure

While the V_T-PEEP plane is a useful tool for visualizing key considerations in avoiding VILI, it is based on the limited premise that safe mechanical ventilation is purely a matter of constraining the lung volume range appropriately. In particular, it assumes that the phenomenon of R/D is determined only by the pressures to which the lung is exposed. In fact, R/D is a function of time as well as pressure [38, 40, 41]. For example, if the airway pressure in a derecruitable lung region is suddenly reduced below the threshold at which its alveoli or airways close, closure does not occur instantaneously but rather manifests over a period of time. Conversely, a closed lung region will not open immediately when subjected to an elevated airway pressure. Furthermore, the rate and amount of closure and reopening for a given pressure change depend on the nature and degree of lung injury [41].

The time dependence of R/D has important clinical implications for the use of recruitment maneuvers, which are prolonged deep inflations designed to open up closed regions of the lung [42]. Recruitment maneuvers would appear to have the obvious rationale of improving gas exchange and reducing tissue stresses by increasing lung compliance. Nevertheless, clinical trials of recruitment maneuvers have been disappointing, so they are not widely used [43] and indeed are not recommended in the current guidelines [44]. This may be because the research community has been asking the wrong question. The debate should not be about "*whether*" recruitment maneuvers should be applied, but rather "*how often*", since their effects are inevitably transitory. The question is complicated, however, because if recruitment maneuvers must be applied frequently to be effective at maintaining a clinically meaningful increase in the level of open lung, they may themselves become an instrument of VILI by increasing the mean tissue stress [40]. R/D dynamics also have important implications for the avoidance of atelectrauma during mechanical ventilation, as discussed below.

Which ventilation strategies are minimally injurious?

Since the ARDSnet trial results were published in 2000 [6], the current standard of care for the ventilatory management of ARDS has been protective low-V_T ventilation. The rationale for this strategy is the reduction in tissue strain that accompanies a reduced V_T, even if the tradeoff is hypercapnia. Prone positioning has also been shown to reduce mortality [7], possibly by allowing the lung to inflate more homogeneously and thus reduce the chances of regional overinflation. It might also produce an altered derecruitment pattern in the lung as a result of a reversed gravitational gradient. It seems unlikely, however, that these strategies collectively represent the best possible, especially since it has yet to be determined how best to set PEEP, despite its self-evident need. Nevertheless, there is no evidence so far that a different strategy based purely on the magnitudes of pressure and volume will be significantly better.

This brings us to the importance of considering R/D dynamics, as mentioned above. The fact that derecruitment takes a finite amount of time to manifest presents the possibility that atelectrauma might be avoided if expiration is sufficiently brief. In other words, time becomes a critical variable to be manipulated in the avoidance of VILI in addition to pressure and/or volume. We illustrate this with a mode of ventilation that exploits time as a parameter - Airway Pressure Release Ventilation (APRV) [45]. APRV is completely specified by four parameters: (1) the duration of inspiration (T_{High}), (2) the duration of expiration (T_{Low}), (3) the constant airway pressure applied during inspiration (P_{High}), and (4) the constant pressure applied during expiration (P_{Low}). Two of these parameters relate to pressure amplitude and two relate to time, and all four can be adjusted independently. The most crucial, however, is T_{Low} because it must be short enough to prevent derecruitment from occurring during expiration; derecruitment results in epithelial surfaces coming into apposition, after which they must undergo the extremely damaging process of being peeled apart again during inspiration [45]. At the same time, T_{Low} must be long enough to achieve adequate alveolar ventilation.

There are a few reports suggesting that APRV is protective in humans [46–48], although not all studies support its superiority over conventional mechanical ventilation [49], which may reflect the critical importance of using an appropriate T_{Low}. Animal studies have shown that avoidance of derecruitment and adequacy of ventilation are simultaneously achieved if expiration is terminated when expiratory flow has fallen to 75% of its peak value [50, 51]. This strategy has been called the Time Controlled Adaptive Ventilation (TCAV) method [52], and has been shown to be protective in terms of reducing lung tissue damage and maintaining blood-gas barrier function in animal models [53, 54]. Studies of TCAV in humans are limited, but there is evidence that it may be protective in some patients [55] provided its parameters are adjusted correctly [56]. Even when APRV is used with longer expirations, its facilitation of spontaneous breathing has been found advantageous even if mortality is not reduced [57].

When T_{Low} is defined by the TCAV method, it varies as the compliance (and thus the emptying time-constant) of the lung varies. T_{Low} thus adapts to changes in lung mechanics in a patient- specific manner by terminating expiration earlier when compliance is low and the emptying time-constant is shorter. This tends to reduce variations in end-expiratory lung volume while also reducing the chances that derecruitment will be able to occur before the next inspiration. The value of T_{High}, which spans most of the ventilatory cycle, can then be chosen to achieve the desired minute ventilation. P_{Low} is typically set to 0 cmH_2O, while P_{High} strikes a balance between being high enough to recruit the lung without causing volutrauma.

Of course, the benefits of a brief expiratory duration are most likely to manifest in a lung that derecruits significantly over the course of a normal expiratory duration because this is the phenomenon that a short T_{Low} is designed to minimize. However, some injured lungs may have significant regions of consolidation that are recalcitrant to being reopened even by very high airway pressures [58], meaning that little R/D takes place over the timescale of a breath. This does not mean that timing is irrelevant, however. On the contrary, keeping T_{Low} short means that the breath cycle is dominated by T_{High}, causing the lung to be subjected to P_{High} the vast majority of the time. Although it may take hours or even days, this can result in the eventual recruitment of even the most refractory lungs [59, 60], thereby eliminating the amplification of tissue stress at the borders between open and consolidated regions of parenchyma [17].

In a series of experimental and computational modeling studies, we have demonstrated that substantial improvements in the preservation of blood-gas barrier integrity can be achieved by taking account of the temporal characteristics of lung volume and pressure over the ventilator cycle, as described above [33, 36, 45, 50, 61, 62]. These studies indicate that TCAV may be protective relative to more conventional ventilation modes in some patients. On the other hand, we cannot claim that TCAV is the *optimal* way to ventilate the injured lung; there may be a better strategy waiting to be discovered. Such strategies might, for example, use expiratory resistors to slow the rate of exhalation, or employ conventional ventilation modes with an inverse inspiration-expiration ratio. These are questions that have yet to be resolved. The success of TCAV thus far suggests, however, that optimal

ventilation of the ARDS lung may not rest on considerations of airway pressure and lung volume alone. Evidence suggests that avoidance of VILI should also take the timing of the ventilatory cycle into account, at least in those patients with recruitable lungs.

Conclusions

Positive pressure mechanical ventilation is frequently a life-saving intervention for patients with ARDS. Even when clearly indicated, however, its application must be tempered by the maxim "*first, do no harm*," so that the injured lung has time to heal on its own. Nevertheless, despite decades of research, it remains unclear exactly how to minimize harm in any particular case. Animal studies indicate that avoidance of VILI requires, above all, avoidance of the atelectrauma that results from cyclic R/D. Accordingly, the path to optimal mechanical ventilation in ARDS must consider not only the amplitudes of the pressures applied to the lung and the resulting inflation volumes but also the temporal nature of the applied pressures. This approach ensures maximal lung recruitment during inspiration while depriving derecruitment of the time it needs to manifest during expiration.

Abbreviations

APRV	Airway pressure release ventilation
ARDS	Acute respiratory distress syndrome
PEEP	Positive end-expiratory pressure
P_{High}	Pressure applied during inspiration in APRV
P_{Low}	Pressure applied during expiration in APRV
R/D	Recruitment and derecruitment
TCAV	Time-controlled adaptive ventilation
T_{High}	Duration of inspiration in APRV
T_{Low}	Duration of expiration in APRV
VILI	Ventilator-induced lung injury
V_T	Tidal volume

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Author contributions

JHTB drafted the manuscript. MKS, DPG and GFN revised the manuscript for critically important content. All authors approved the final version to be published.

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Data availability

All materials available from the communicating author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable (no human or animal data).

Consent for publication

Not applicable (no personal data).

Competing interests

JHTB is a scientific advisor for and shareholder in Oscillavent, Inc. (Iowa) and Respiratory Sciences, Inc. (Minnesota), and consults for Chiesi USA, Inc. MKS has delivered lectures for and received an educational research grant (November 2020) from Dräger Medical Systems, Inc. GFN has received honoraria and/or travel reimbursement at event(s) sponsored by Dräger Medical Systems, Inc., outside of the published work. GFN has lectured for Intensive Care On-line Network, Inc. (ICON).

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